Proposed Decision Memo for Screening Computed Tomography Colonography (CTC) for Colorectal Cancer (CAG-00396N)

Decision Summary

The Centers for Medicare and Medicaid Services (CMS) proposes the following:

The evidence is inadequate to conclude that CT colonography is an appropriate colorectal cancer screening test under §1861(pp)(1) of the Social Security Act. CT colonography for colorectal cancer screening remains noncovered.

We are requesting public comments on this proposed determination pursuant to Section 1862(l) of the Social Security Act. After considering the public comments, we will make a final determination and issue a final decision memorandum. As with all national coverage analyses, the public may submit comments or additional evidence that cause us to reassess our evidentiary review and arrive at different conclusions. If that should occur during finalization of this decision memorandum and we determine that CT colonography is clinically effective, then we would need to determine, using current or additional cost information, if CT colonography is cost effective. We are asking for public comment on the cost effectiveness of screening CT colonography for the Medicare population if we were to alter our clinical decision.

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Proposed Decision Memo

To: Administrative File CAG-00396N
Screening Computed Tomographic Colonography (CTC) for Colorectal Cancer

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Subject: Proposed Coverage Decision Memorandum for Screening Computed Tomographic (CT) Colonography for Colorectal Cancer

Date: February 11, 2009

I. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes the following:

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II. Background

Colorectal cancer (CRC) remains one of the three most common cancers and a leading cause of cancer deaths in the United States. Unlike many others, early detection and intervention have been shown to improve survival in randomized trials on fecal occult blood tests. Colorectal cancer screening is recommended universally. Since 1998, Medicare has covered several CRC screening tests such as fecal occult blood tests, flexible sigmoidoscopy, and optical colonoscopy for average risk individuals. While colorectal cancer remains a leading cancer among women and men, the recent declines in both U.S. incidence and mortality as reported by Jemal and colleagues (2008) are encouraging. The authors noted: “The accelerated decline in the colorectal cancer incidence rate since 1998 may be associated with increased use of colorectal cancer screening, which prevents cancer through removal of precancerous adenomatous polyps. Between 2000 and 2005, the percentage of adults aged 50 years and older who reported having had colonoscopy increased from 20% to 39%, whereas the percentage reporting testing for fecal occult blood decreased from 17% to 12%. Overall, the use of colorectal screening among adults 50 years and older increased from 27% in 1987 to 50% in 2005.”

In recent years, computed tomographic (CT) colonography, also referred to as virtual colonoscopy, has been studied as a CRC screening test. After full purgatory bowel preparation similar to the preparation used for optical colonoscopy, stool and fluid tagging with oral contrast, and room air or carbon dioxide insufflation of the colon, a CT scan is performed in both supine and prone positions while the patient is fully conscious and produces images of the colon and rectum to assess the presence or absence of structural lesions such as polyps and cancer. It may be considered an intermediate test since it does not have a direct mechanism for removal of polyps. Individuals found to have clinically important polyps must be referred for optical colonoscopy to remove the polyps and accomplish cancer prevention.

In the Balanced Budget Act of 1997, Pub. L. No. 105-33, §4104 (August 5, 1997), Congress gave the Secretary of Health and Human Services the authority to cover additional CRC screening tests as determined appropriate, in consultation with appropriate organizations. CMS used this authority in 2003 to provide coverage for the fecal immunoassay test after assessing its specific screening test parameters and net health benefits (http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=87). See Medicare National Coverage Determination Manual at sections 190.34 and 210.3.

As we noted in our decision on the fecal immunoassay test, the consideration of a screening test involves a number of factors unlike that of diagnostic tests and therapeutic interventions because screening is performed on individuals who do not have symptoms. Since individuals undergoing screening are asymptomatic, the threshold of “first doing no harm” is raised. In their classic publication, Cochrane and Holland (1971) emphasized this distinction when they noted: “We believe there is an ethical difference between everyday medical practice and screening. If a patient asks a medical practitioner for help, the doctor does the best he can. He is not responsible for defects in medical knowledge. If, however, the practitioner initiates screening procedures, he is in a very different situation. He should, in our view, have conclusive evidence that screening can alter the natural history of disease in a significant proportion of those screened.” Cochrane and Holland further laid out the analytic framework for the validation of screening test methods which remains in use today and will be utilized in this decision.

In May 2008 following the completion and publication of several large studies on screening CT colonography and updated CRC screening guidelines, CMS initiated this national coverage analysis to evaluate the evidence on CT colonography and to determine if the evidence is sufficient for Medicare coverage. This analysis does not address the use of CT colonography as a diagnostic test. In November 2008, a Medicare Evidence Development & Coverage Advisory Committee (MedCAC) meeting was held “to discuss the various kinds of evidence that are useful to support requests for Medicare coverage in this field.” Notice, 73 Fed. Reg. 55848 (Sept. 26, 2008).

III. History of Medicare Coverage

The Balanced Budget Act of 1997, Pub. L. No. 105-33; § 4104 (1997), established coverage for colorectal cancer screening procedures under Medicare Part B, effective January 1, 1998. Medicare currently covers (1) annual FOBTs, (2) flexible sigmoidoscopy every 4 years, (3) screening colonoscopy for persons at average risk for colorectal cancer every 10 years[i], or for persons at high risk for colorectal cancer every 2 years[ii], (4) barium enema every 4 years as an alternative to flexible sigmoidoscopy or colonoscopy, and (5) other procedures the Secretary finds appropriate based on consultation with appropriate organizations. See 42 C.F.R. §410.37; 62 Fed. Reg. 59079-59082, 59100-59101 (Oct. 31, 1997).

In the Physician Fee Schedule Final Rule for 2003, CMS amended the FOBT screening regulation definition at 42 C.F.R. § 410.37 (a) (2) to provide coverage of either (1) a guaiac-based FOBT, or (2) other tests as determined by the Secretary through a national coverage determination. See 67 Fed. Reg. 79966, 80040 (Dec. 31, 2002). On November 4, 2003, CMS issued a final Decision Memorandum indicating that effective November 4, 2003, Medicare would cover a screening immunoassay FOBT on an annual basis as an alternative to the guaiac-based FOBT.

In the same rulemaking, CMS also amended the colorectal cancer screening test regulation at 42 C.F.R. § 410.37 (a) (1) (v) to provide that in addition to the screening test options already covered under the regulation, it could include coverage of additional colorectal cancer screening tests through issuance of a national coverage determination.

Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category under Part A or Part B as a prerequisite to Medicare coverage. Congress has specifically authorized coverage of certain colorectal cancer screening tests under Part B of the Medicare program and has consistently made necessary conforming changes in order to ensure that payments are made. Colorectal Cancer Screening Tests have a benefit category under § 1861(s)(2)(R) and § 1861(pp) of the Social Security Act. Specifically, CMS is using the authority under § 1861(pp)(1)(D) and 42 C.F.R. § 410.37(a)(1)(v) to determine whether the scope of the CRC screening benefit should be expanded to include coverage of the CT colonography screening test.

IV. Timeline of Recent Activities

May 19, 2008	CMS initiates this national coverage analysis for the use of screening CTC for colorectal cancer. The public has 30 days to submit comments on this topic. CMS considers all public comments, and is particularly interested in clinical studies and other scientific information related to the technology under review. We are especially interested as to the types of studies needed if the evidence is determined to be premature for coverage or if the appropriate frequency interval is uncertain.
November 19, 2008	CMS convened the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) to review the available evidence on the use of CTC as a screening test for colorectal cancer for average risk individuals, including test characteristics, screening frequency, cost effectiveness, safety and training requirements.
February 11, 2009	CMS posts a proposed decision memorandum and the 30 day public comment period begins.

V. FDA Status

Currently, CT imaging systems and post-processing software for colon imaging go through the FDA 510(k) process to obtain clearance for commercial distribution. To obtain 510(k) clearance, the sponsor must demonstrate that the device is substantially equivalent to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act), or to devices that are currently legally on the market.

CT devices were on the market prior to the passage of the Medical Device Amendments. They were originally indicated for general cross sectional imaging of the body. This includes the colon and other specific organs. Subsequent modifications based on either additional built in processing or on post processing have expanded the breadth of CT images and with that their use. CT colonography is an example of this process. Originally, colon images were viewed as a series of individual cross sectional images. With improved processing, these images can be combined into a fly-through presentation; this has led to CT colonography mimicking an optical colonoscopy. The fly-through presentation clearance was based on the re-presentation of existing data and not on new information. There are also companies developing colon CAD devices, which may assist the radiologist in the detection of potential polyps in a CT colonography.

Whole Body CT Imaging (see http://www.fda.gov/cdrh/ct/)

Some medical imaging facilities are currently promoting whole-body CT imaging as a preventive or proactive healthcare measure to healthy, asymptomatic individuals. At this time the FDA knows of no data demonstrating that whole-body CT screening is effective in detecting any particular disease early enough for the disease to be managed, treated, or cured and advantageously spare a person at least some of the detriment associated with serious illness or premature death. Any such presumed benefit of whole-body CT screening is currently uncertain, and such benefit may not be great enough to offset the potential harms such screening could cause. Statements by whole body CT imaging facilities that imply FDA "approval," "clearance," or "certification" of whole body CT for screening of asymptomatic patients misrepresent the actual situation. FDA has never approved or cleared or certified any whole body CT system specifically for use in screening of asymptomatic patients.

CT Colonography

CT imaging devices (both hardware and software) presenting fly-through imaging of the colon have been cleared for colon cancer screening. There are numerous articles and opinions in the literature indicating that optical colonoscopy and CT colonography are nearly equivalent in terms of effectiveness and several medical and health organizations have endorsed its use.

The FDA has given 510(k) clearance for the following post-processing software devices used with CT of the colon.

Device Name: V3D Colon, Revision 1.3, Viatronix, Inc.
510(k) Number: K040126 (available at:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/PMNSimpleSearch.cfm?db=PMN&ID=K040126)
Decision Date: 04/19/2004
Decision: Substantially equivalent

Device Name: Colon CAR™ Release 1.2, Medicsight PLC.
510(k) Number: K042674 (available at:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/PMNSimpleSearch.cfm?db=PMN&ID=K042674)
Decision Date: 10/19/2004
Decision: Substantially equivalent

Device Name: CT Colonography II, General Electric Medical Systems
510(k) Number: K041270
(available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/PMNSimpleSearch.cfm?db=PMN&ID=K041270)
Decision Date: 5/27/2004
Decision: Substantially equivalent

Device Name: syngo Colonography software package with extended functionality, Siemens Ag, Medical Solutions
510(k) Number: K042605
(available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/PMNSimpleSearch.cfm?db=PMN&ID=K042605)
Decision Date: 10/8/2004
Decision: Substantially equivalent

Medicsight PLC has also submitted an application to the FDA seeking 510(k) clearance of ColonCAD™ (available at: http://investor.medicsight.com/releasedetail.cfm?ReleaseID=347957).

VI. General Methodological Principles

When making national coverage decisions concerning the scope of the CRC screening benefit under Medicare Part B, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that a test is appropriate for general screening in the Medicare population. The critical appraisal of the evidence enables us to determine what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the screening test is appropriate and how it compares to existing covered tests. In general, features or clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will not be made available to the public. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

Since screening is conducted on asymptomatic individuals, the analytic framework for screening tests involves consideration of several different factors compared to diagnostic tests and therapeutic interventions. Fortunately, the evaluation of screening tests has been standardized and accepted. Cochrane and Holland (1971) reported: “The value of a screening test may be assessed according to the following criteria:

i. *Simplicity*. In many screening programmes more than one test is used to detect one disease, and in a multiphasic programme the individual will be subjected to a number of tests within a short space of time. It is therefore essential that the tests used should be easy to administer and should be capable of use by para-medical and other personnel.
ii. *Acceptability*. As screening is in most instances voluntary and a high rate of co-operation is necessary in an efficient screening programme, it is important that tests should be acceptable to the subjects.
iii. *Accuracy*. The test should give a true measurement of the attribute under investigation.
iv. *Cost*. The expense of screening should be considered in relation to the benefits resulting from the early detection of disease, i.e., the severity of the disease, the advantages of treatment at an early stage and the probability of cure.
v. *Precision (sometimes called repeatability)*. The test should give consistent results in repeated trials.
vi. *Sensitivity*. This may be defined as the ability of the test to give a positive finding when the individual screened has the disease or abnormality under investigation.
vii. *Specificity*. This may be defined as the ability of the test to give a negative finding when the individual screened does not have the disease or abnormality under investigation.”

In this coverage analysis, we considered CT colonography studies and evidence that were published after 2003 since systematic reviews of earlier studies and evidence based guidelines (USPSTF, 2002; Winawer, 2003; U.S. Multisociety Task Force, 2003) did not support routine screening use. As Cochrane and Holland (1971) noted, health outcomes are important in the consideration of screening tests. However, even the most recent studies have focused primarily on test characteristics and have not considered survival. Intermediate outcomes, such as increase in CRC screening or reduction of normal optical colonoscopies have not been reported.

Literature Search

CMS searched PubMed from January 2003 to October 2008. General keywords included screening computed tomographic colonography and virtual colonoscopy. Initially, we searched for studies on asymptomatic, average risk individuals that presented original data using multislice CT, examined health outcomes and were published in peer-reviewed English language journals. Since no study met the criteria for health outcomes, the search was expanded to include technology assessments, meta-analysis, reviews, and studies that reported only test characteristics compared to optical colonoscopy. Abstracts were excluded. Using these general parameters, 6 original studies and 6 reviews were found.

B. Discussion of evidence reviewed

1. Evidence Questions

Our determination of whether CT colonography is an appropriate screening test under Medicare involves consideration of test parameters and health outcomes. For this NCD, the questions of interest are:

a. Is the evidence sufficient to determine that CT colonography is a valuable screening test for colorectal cancer for average risk Medicare individuals compared to optical colonoscopy?

b. Is the evidence sufficient to conclude that the use of CT colonography improves health outcomes for colorectal cancer screening in average risk individuals compared to optical colonoscopy?

2. External Technology Assessments

Whitlock EP, Lin JS, Liles E, Bell TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2008;149:638-658.

Whitlock and colleagues reported the results of a systematic review of colorectal cancer screening tests. For CT colonography, 4 studies with 4312 average risk individuals were reviewed. The authors noted: “In settings with sufficient quality control, CT colonography is as sensitive as colonoscopy for large adenomas and colorectal cancer. Uncertainties remain for smaller polyps and frequency of colonoscopy referral.” They concluded: “Computed tomographic colonography seems as likely as colonoscopy to detect lesions 10 mm or greater but may be less sensitive for smaller adenomas. Potential radiation-related harms, the effect of extracolonic findings, and the accuracy of test performance of CT colonography in community settings remain uncertain.”

Zauber AG, Knudsen AM, Rutter CM, Lansdorp-Vogelaar I, Savarino JE, van Ballegooijen M, Kuntz KM. Cost-effectiveness of CT colonography to screen for colorectal cancer. Report to AHRQ from the Cancer Intervention and Surveillance Modeling Network (CISNET) for MISCAN, SimCRC, and CRC-SPIN Models. Available at: http://www.cms.hhs.gov/determinationprocess/downloads/id58TA.pdf

Zauber and colleagues reported the results of a cost-effectiveness analysis performed using 3 established colorectal cancer screening models. They noted: “Based on the analyses from three microsimulation models, screening for CRC with CT colonography every 5 years with referral of individuals with a 6 mm or larger lesion to colonoscopy provides a benefit in terms of life-years gained that is comparable to that of five-year flexible sigmoidoscopy with annual FOBT and slightly lower than colonoscopy screening every 10 years. The cost of CT colonography relative to the benefit derived and to the availability and costs of other CRC screening tests, would need to be in the range of $108 to $205 to be a cost-effective alternative to all other available screening modalities, and in the range of $179 to $237 to be cost-effective compared to colonoscopy screening with CMS payment of approximately $500 for colonoscopy without polypectomy and $650 for colonoscopy with polypectomy.”

Washington State Health Care Authority. CT colonography for colorectal cancer screening. 2008. Available at http://www.hta.hca.wa.gov/vc.html.

The Washington State Health Technology Clinical Committee (HTCC), an independent committee of 11 health practitioners, determines how selected health technologies are covered by several state agencies, reviewed CT colonography and does not provide coverage. In their assessment (prepared by the Institute for Clinical and Economic Review) they noted: “In conclusion, given the current standard for performance, CT colonography is nearly as or equally sensitive as optical colonoscopy for detection of lesions > 10 mm on a per patient basis. It is somewhat less sensitive on a per patient basis for smaller lesions or for detecting individual lesions. It seems likely that the majority of current sources of observer error can be overcome through use of standardized and stringent methods for bowel cleansing, use of fecal tagging and contrast media, and use of computer assisted methods for scan interpretation. Observer training is a critical component for reducing perceptual errors. CT colonography is relatively safe and existing data suggest that CT colonography is acceptable to patients, although it is unclear whether implementation of CT colonography to the colorectal screening armamentarium would result in increased rates of colorectal screening and overall earlier detection of colorectal cancer in the general population.”

Winawer SJ. Colorectal cancer screening. Best Practice & Research Clinical Gastroenterology 2007;21:1031–1048.

Winawer reported the results of a systematic review on colorectal cancer screening. He noted: “reconstructions of the colonic lumen (‘virtual colonoscopy’). The procedure requires air insufflation for colonic distension to maximal tolerance (approximately two litres of room air or carbon dioxide) and cathartic bowel preparation. More recently preparations that involve the ingestion of an oral contrast agent days prior to the study (‘faecal tagging’) have been for electronic (computer) subtraction of stool and liquid. Meta-analysis of studies using CTC for the detection of colorectal polyps and cancer showed high sensitivity (93%) and high specificity (97%) of this technique for polyps of 10 mm or larger. However, for large and medium sized polyps combined (six millimetres or larger) the average sensitivity decreased to 86% with a specificity of 86%. When polyps of all sizes were included, studies were too heterogeneous in sensitivity (range, 45%–97%) and specificity (range, 26%–97%). While sensitivity of CTC for cancer and large polyps is satisfactory, detection of polyps in the six to nine millimetre size range is not satisfactory. Another important drawback of CTC for screening patients at increased risk is that flat lesions are missed. Major complications are rare. CTC outcomes seem to depend largely on the expertise of the radiologists and the techniques used. CTC techniques are improving and seem to perform at a clinically useful level in some centres. However, a major disadvantage of CTC for its use as a screening procedure is the repeated patient exposure to substantial doses of ionising radiation. Lately, multidetector or multislice CT technology shortens scan time and reduces radiation dose while preserving high spatial resolution. Furthermore, the issue of when to refer patients for colonoscopy is unresolved. This has an enormous impact on the cost of the procedure. Another disadvantage is that the examination requires a complete bowel preparation. If patients need colonoscopy, they must undergo a second bowel preparation. Finally, extraintestinal findings can lead to evaluation and increased costs.”

Rosman AS, Korsten MA. Meta-analysis comparing CT colonography, air contrast barium enema, and colonoscopy. American Journal of Medicine 2007;120:203-210.

Rosman and Korsten reported the results of a meta-analysis of 30 studies (total number of individuals was not reported) published from 1996-2005. Studies were eligible for inclusion if all individuals received both CT colonography and colonoscopy and the studies reported per patient test characteristics. Studies were excluded if they had small sample sizes (n< 5) or excess numbers of cancers.

The pooled per patient sensitivities of CT colonography were 74% (95% CI, 66%-81%) overall, 56% (95% CI, 42%-70%) for polyps < 6mm, 63% (95% CI, 52%-75%) for polyps 6-10mm, and 82% (95% CI, 76%-88%) for polyps > 10mm. The pooled per patient specificity of CT colonography was 77% (95% CI, 69%-86%) overall. The authors concluded: “CT colonography has a reasonable sensitivity and specificity for detecting large polyps but was less accurate than endoscopic colonoscopy for smaller polyps. Thus, CT colonography may not be a reasonable alternative in situations in which a small polyp may be clinically relevant.” In this review, studies on high risk symptomatic patients were included.

Mulhall BP, Veerappan GR, Jackson JL. Meta-analysis: computed tomographic colonography. Ann Intern Med 2005;142:635-650.

Mulhall and colleagues reported the results of a systematic review of 33 studies (6393 individuals) published from 1975 to 2005. Inclusion criteria were prospective, blinded design, adult patients, and CT scans with insufflation.

The pooled per patient sensitivities of CT colonography were 70% (95% CI, 53%-87%) overall, 48% (95% CI, 25%-70%) for polyps < 6mm, 70% (95% CI, 55%-84%) for polyps 6-9mm, and 85% (95% CI, 79%-91%) for polyps > 9mm. The pooled per patient specificity of CT colonography was 86% (95% CI, 84%-88%) overall. The authors concluded: "Computed tomographic colonography is highly specific, but the range of reported sensitivities is wide. Patient or scanner characteristics do not fully account for this variability, but collimation (x-ray beam thickness), type of scanner, and mode of imaging explain some of the discrepancy. This heterogeneity raises concerns about consistency of performance and about technical variability. These issues must be resolved before CT colonography can be advocated for generalized screening for colorectal cancer." In this review, studies on high risk symptomatic patients were included.

3. Internal Technology Assessment

Johnson CD, Chen MH, Toledano AY, Heiken JP, Dachman A, Kuo MD, et al. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med 2008;359:1207-1217.

Johnson and colleagues reported the results of a study of 2600 adults at 15 centers "to assess the accuracy of CT colonography in detecting histologically confirmed, large colorectal adenomas and cancers (≥ 10 mm in diameter), with optical colonoscopy (the current clinical standard for colorectal cancer screening) and histologic review used as the reference standard." All participants were 50 years of age or older, did not have symptoms of major bowel diseases, and were scheduled for routine colonoscopy. The study was conducted at 15 clinical sites in the United States. Exclusion criteria includes melena, hematochezia, lower abdominal pain, inflammatory bowel disease, familial polyposis, colonoscopy in past 5 years, complications from prior colonoscopy, anemia and a positive fecal occult blood test. The primary endpoint was "detection by CT colonography of histologically confirmed large adenomas and adenocarcinomas (10 mm in diameter or larger) that had been detected by colonoscopy."

CT colonography was performed using at least 16 row multidetector CT scanners with colonic carbon dioxide insufflation and one milligram of subcutaneous glucagons. Preparation included laxative purgation, fluid and stool tagging with oral contrast.

Of the 2600 participants, complete data were available for 2531 (97%). Of these, 89% were considered at average risk for colorectal cancer. Mean age was 58 years. Men comprised 48% of the 2531. In per-patient analysis, the authors reported sensitivity, specificity, positive predictive value and negative predictive value for at least one lesion ≥ 6mm of 0.78, 0.88, 0.40 and 0.98, respectively; and for at least one lesion ≥ 10 mm of 0.90, 0.86, 0.23, and 0.99, respectively. In per-polyp analysis, the authors reported sensitivity for lesions ≥ 5mm of 0.70 and for lesions ≥ 10mm of 0.84. The authors reported that "extracolonic findings were observed in 66% of the participants; however, only 16% were deemed to require either additional evaluation or urgent care." They concluded: "In this study of asymptomatic adults, CT colonographic screening identified 90% of subjects with adenomas or cancers measuring 10 mm or more in diameter. These findings augment published data on the role of CT colonography in screening patients with an average risk of colorectal cancer." Participants were recruited from individuals already scheduled for routine colonoscopy. Segmental unblinding was not used. Repeat colonoscopy was advised for individuals with polyps ≥ 10mm on CT scans but not seen on colonoscopy. Individuals with a history of polyps or cancer were not specifically excluded and comprised 1% (34/2531) of the study. There was no follow up for health outcomes, extracolonic findings or subsequent testing. Radiologists participating in the study had specific training and were required to detect ≥ 90% of polyps ≥ 10mm on image testing.

Graser A, Stieber P, Nagel D, Schaefer C, Horst D, Becker Cr, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy, and fecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut (Online) 2008;doi:10.1136/gut.2008.

Graser and colleagues presented the results of a comparative study of 311 asymptomatic average risk adults "to compare the performance characteristics of five different screening tests in parallel for the detection of advanced colonic neoplasia." Participants were "over 50 years of age and free of symptoms of colonic diseases like melaenic stools, hematochezia, diarrhoea, relevant changes in stool frequency, or abdominal pain." Exclusion criteria included history of inflammatory bowel disease, family history for colorectal cancer and severe heart or lung disease. CT colonography was performed using 64 channel multidetector scanners with bowel preparation, oral contrast and CO2 insufflation. Colonoscopy was performed after CT colonography with segmental unblinding.

Of the 311 adults enrolled, 4 were excluded due to incomplete colonoscopy or withdrawal from the study. Of the remaining 307, 221 adenomas were detected in 113 participants. Of the adenomas, 147 were ≤ 5mm; 41 were 6-9mm; and 33 were ≥ 10mm in size. Of the 46 advanced lesions, 7 were ≤ 5mm; 6 were 6-9mm; and 33 were ≥ 10mm in size. For CT colonography, per polyp sensitivity was 70.1% for all adenomas; 59.2% for adenomas < 6mm; 90.2% for 6-9mm; and 93.9% for > 9mm. For all adenomas, per person sensitivity was 84.1% and specificity was 47.4%. For adenomas > 5mm, per person sensitivity was 91.3% and specificity was 93.1%. For adenomas > 9mm, per person sensitivity was 92.0% and specificity was 97.9%.

On polyp size, the authors noted: "The relevance of diminutive and small polyps 1 – 9 mm in size has recently become a controversial topic. At least 20 – 30% of the average-risk asymptomatic population above age 50 carry adenomatous polyps. The majority of these are smaller than 10 mm. However, controversy exists as to the likelihood that small adenomas harbour significant advanced histology or progress to colorectal cancer. This has important implications on reporting and follow-up. A recent consensus proposal for CT colonography reporting suggested that diminutive polyps do not need to be reported and patients with 2 or less polyps <10 mm are recommended to undergo follow up CT colonography after 3 years rather than immediate colonoscopy for polypectomy, which is recommended for large polyps or if 3 or more small polyps are present. As small and medium size lesions may contain advanced histology, following this recommendation might lead to an increase in colorectal cancer incidence and mortality."

The authors concluded: “High resolution and low dose CTC is feasible for colorectal cancer screening and reaches comparable sensitivities to colonoscopy for polyps >5 mm. For patients who refuse full bowel preparation and OC or CTC, FS should be preferred over stool tests. However, in case stool tests are performed, FIT should be recommended rather than FOBT.”

Cornett D, Barancin C, Roeder B, Reichelderfer M, Frick T, Gopal D, et al. Findings on optical colonoscopy after positive CT colonography exam. Am J Gastroenterol 2008;103:2068–2074.

Cornett and colleagues reported the results of a study “to evaluate the findings on optical colonoscopy (OC) in patients who had a positive screening CTC examination and to assess the number, size, shape, location, and pathology of polyps seen on OC but missed on CTC.” A total of 159 patients with polyps > 5mm seen on CT colonography underwent optical colonoscopy. CT scans were performed using 8 or 16 channel machines with oral contrast and colonic insufflation. Polyps ≤ 5mm were not reported by CT colonography per protocol. Mean age was 59.3 years. Men comprised 51% of the participants.

Of the 359 polyps detected on colonoscopy, 230 polyps were seen and reported on CT colonography (sensitivity = 64%). Of the 137 polyps seen on OC but not CT colonography, 99 (72%) were < 6mm, 27 (20%) were 6-9mm, and 11 (8%) were > 9mm in size. Of the 159 participants, 8 (5%) were considered false positives. The authors concluded: “CT colonography has adenoma miss rates similar to miss rates historically found with optical colonoscopy, with most missed adenomas being <10 mm and sessile in shape.” In this study, the results of the CT colonography were available to the colonoscopists prior to the optical colonoscopy.

Kim DH, Pickhardt PJ, Taylor AJ, Leung WK, Winter TC, Hinshaw JL, et al. CT Colonography versus colonoscopy for the detection of advanced neoplasia. N Engl J Med. 2007;357:1403-12.

Kim and colleagues reported the results of a study “to compare computed tomographic colonography (CTC) and optical colonoscopy (OC) when applied to the same general screening population.” Participants in a CT colonography screening program (n=3120) were compared to participants in a separate colonoscopy screening program (n=3163). Participants were referred by the same groups of primary care providers. Exclusion criteria included polyp surveillance, history of a bowel disorder, and hereditary nonpolyposis colorectal cancer syndrome. Main outcomes included detection of advanced neoplasia and total number of polyps removed. CT colonography was performed using 8 or 16 multidetector scanners with cathartic bowel preparation, oral contrast and carbon dioxide insufflation. Mean age was 57 years in the CT colonography group and 58 years in the colonoscopy group. Men comprised about 56% of both groups. Most participants did not have symptoms (about 98% in both groups) and did not have a family history of colorectal cancer (about 95% in the CT colonography group and 92% in the colonoscopy group).

There were 123 (4%) and 121 (4%) advanced neoplasms identified during CT colonography and colonoscopy screening, respectively. Of these, 103 (3%) in each group were advanced adenomas ≥ 10 mm. The test positive rate of the CT colonography group was 12.9%. Extracolonic findings (C-RADS class E2-E4) were present in 58% of the participants in the CT colonography group. The authors concluded: “Primary CTC and OC screening strategies resulted in similar detection rates for advanced neoplasia, although the numbers of polypectomies and complications were considerably smaller in the CTC group. These findings support the use of CTC as a primary screening test before therapeutic OC.” Participants were not randomly assigned to groups. The decision process on the choice of screening by participants or primary care providers was not described. There was no follow up for health outcomes, extracolonic findings or subsequent testing.

Macari M, Bini EJ, Jacobs SL, Naik S, Lui YW, Milano A, et al. Colorectal polyps and cancers in asymptomatic average-risk patients: evaluation with CT colonography. Radiology 2004;230:629–636.

Macari and colleagues reported the findings of a case series of 69 men “to compare the results at thin-section multi–detector row CT colonography with those at conventional colonoscopy in the evaluation of colorectal polyps and cancer in a group of asymptomatic average-risk patients.” Participants were men older than 50 years who were scheduled to undergo screening colonoscopy and had no colorectal symptoms, prior polyps or family history of cancer. Main outcome was detection of colorectal polyps. Mean age was 55 years.

CT colonography was performed using a 4 detector CT scanner with bowel preparation and colonic insufflation. In per polyp analysis, the authors reported sensitivity of 60% (12/20) for polyps ≥ 6mm and 100% (3/3) for polyps ≥ 10mm. In per patient analysis, the authors reported specificity of 90% (26/29). The authors concluded: “In patients at average risk for colorectal cancer, CT colonography is a sensitive and specific screening test for detecting polyps 10 mm or larger; the sensitivity for detecting smaller polyps is decreased.” Adverse outcomes were not reported. Health outcomes were not reported.

Pickhardt PJ, Choi RJ, Hwang I, Butler JA, Puckett ML, Hildebrandt HA, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med 2003;349:2191-200.

Pickhardt and colleagues reported the results of a study of 1233 asymptomatic adults at 3 centers “to evaluate the performance characteristics of virtual colonoscopy in a typical asymptomatic screening population.” Average risk individuals aged 50 to79 years and individuals with a family history of colorectal cancer aged 40 to 79 years were recruited through referrals for screening colonoscopy. Exclusion criteria included positive FOBT, anemia, rectal bleeding, history of polyps or cancer, and optical colonoscopy within previous 10 years. Main outcome was the detection of adenomatous polyps ≥ 6mm in diameter. CT scans were performed using 4 or 8 channel machines with colonic preparation, oral barium and colonic insufflation. Segmental unblinding was used. Mean age was 57.8 years. Men comprised 59% of the study population.

For polyps ≥ 6mm, the authors reported per patient sensitivity and specificity of 88.7% and 79.6%, respectively. For polyps ≥ 10mm, the authors reported per patient sensitivity and specificity of 93.8% and 96%, respectively. The per polyp sensitivity was 85.7% for polyps≥ 6mm and 92.2% ≥ 10mm. Total number of extracolonic findings was not reported but about 18% had findings that were considered of high or moderate clinical importance. There were "no clinically significant complications." The authors noted that "at a threshold of 6 mm, 70.3 percent of the patients in our study would not have been sent for immediate polypectomy." They concluded: "CT virtual colonoscopy with the use of a three-dimensional approach is an accurate screening method for the detection of colorectal neoplasia in asymptomatic average risk adults and compares favorably with optical colonoscopy in terms of the detection of clinically relevant lesions."

4. MEDCAC

A meeting of the Medicare Evidence Development and Coverage Advisory Committee was held on November 19, 2008 to publicly discuss the available evidence. Information about the meeting, including the technology assessments commissioned by CMS and AHRQ, panel questions and voting results and transcript are available on our website at http://www.cms.hhs.gov/mcd/viewmcac.asp?where=index&mid=45.

The technology assessments by Whitlock et al. and Zauber et al. were presented, and are summarized in a previous section of this document.

The panel voted on seven questions using a 1 – 5 scale with 1 representing a "no confidence" vote and 5 representing a "high confidence" vote. The scores of the eleven voting panel members were recorded and the average was calculated. The first question asked whether there was sufficient evidence to determine the sensitivity and specificity of screening CTC using at least 16 slice scanners for average risk individuals compared to optical colonoscopy for polyps in four size categories that are (1) less than 6 mm, (2) 6 to less than 10 mm, (3) equal to or greater than 6 mm, and (4) equal to or greater than 10 mm. The average voting member score was 1.18, 3.18, 3.55, and 4.73, respectively. On the 1 to 5 scale, a score of 3 represents a vote of "equivocal" and a score of 4 represents a vote of "moderate confidence." The second question asked whether there was sufficient evidence to determine the net health benefits of screening CTC using at least 16 slice scanners for polyps in the same four size categories – (1) less than 6 mm, (2) 5 to less than 10 mm, (3) equal to or greater than 6 mm, and (4) equal to or greater than 10 mm. The average score of the voting members on this question was 1.55, 2.45, 3.09, and 3.91, respectively. Question three asked whether the previous evidence and modeling for the treatment of polyps discovered using other screening modalities can be applied to polyps discovered using screening CTC. The average voting members score was 4.36 on this question. Regarding the panel's confidence regarding whether the evidence demonstrates that screening CTC results in a net health benefit for Medicare beneficiaries similar to optical colonoscopy (question four) (that is, net health benefits include the decrease in morbidity and mortality from the identification and removal of polyps balances with the risks of the procedure and the identification of extracolonic abnormalities, but not cost) the average score was 3.36. At current Medicare prices, question five asked panel members how confident were they that screening CTC has a similar ratio of cost per Life Years Saved as compared to optical colonoscopy. The average panel vote was 1.55 on that question or midway between 1 for "no confidence" and 2 for "little confidence." In question six, the panel voted 2.00 as to whether the evidence demonstrated that the use of CTC screening in the average risk population would increase overall colorectal cancer screening rates in that population. Finally, question seven asked the panel whether there was sufficient evidence to determine the appropriate CTC guidelines for (1) referral for polyp removal and (2) frequency of screening. The average voting member score was 3.55 and 2.27, respectively, on the two parts to the question.

5. Evidence-based guidelines

U.S. Preventive Services Task Force (USPSTF). Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008;149:627-637.

The USPSTF published a revision to their 2002 colorectal screening guidelines. They concluded: “The USPSTF recommends screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 years and continuing until age 75 years. The risks and benefits of these screening methods vary. (A recommendation) The USPSTF recommends against routine screening for colorectal cancer in adults 76 to 85 years of age. There may be considerations that support colorectal cancer screening in an individual patient. (C recommendation) The USPSTF recommends against screening for colorectal cancer in adults older than age 85 years. (D recommendation) The USPSTF concludes that the evidence is insufficient to assess the benefits and harms of computed tomographic colonography and fecal DNA testing as screening modalities for colorectal cancer. (I statement).”

6. Professional Society Position Statements

McFarland E, Levin B, Lieberman D, Pickhardt P, Johnson G, Glick SN, et al. Revised colorectal screening guidelines: Joint effort of the American Cancer Society, U.S. Multisociety Task Force on Colorectal Cancer, and American College of Radiology. Radiology 2008;248:717-720.

This editorial summarized the guidelines reported by Levin and colleagues (below).

Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, et al.
Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008;58:130-160. [Also published in Gastroenterology 2008;134:1570–1595.]

These guidelines were developed using an evidence-based approach coupled with expert opinion when “the evidence was insufficient or lacking to provide a clear, evidence based conclusion.” For CT colonography (CTC), the authors wrote the following excerpt:

“In terms of detection of colon cancer and advanced neoplasia, which is the primary goal of screening for CRC and adenomatous polyps, recent data suggest CTC is comparable to OC for the detection of cancer and polyps of significant size when state-of-the-art techniques are applied. In previous assessments of the performance of CTC, the ACS concluded that data were insufficient to recommend screening with CTC for average-risk individuals. Based on the accumulation of evidence since that time, the expert panel concludes that there are sufficient data to include CTC as an acceptable option for CRC screening. Screening of average-risk adults with CTC should commence at age 50 years. The interval for repeat exams after a negative CTC has not been studied and is uncertain. However, if current studies confirm the previously reported high sensitivity for detection of cancer and of polyps ≥6 mm, it would be reasonable to repeat exams every 5 years if the initial CTC is negative for significant polyps until further studies are completed and are able to provide additional guidance. Until there is more research on the safety of observation, patients whose largest polyp is 6 mm or greater should be offered colonoscopy (CSPY). CTC surveillance could be offered to those patients who would benefit from screening but either decline CSPY or are not good candidates for CSPY for one or more reasons. However, if CSPY is contraindicated because the patient is not likely to benefit from screening due to life-limiting comorbidity, then neither CTC nor any other CRC screening test would be appropriate.”

American Gastroenterological Association (AGA) 2008 Position Statement. Available at: http://www.gastro.org/wmspage.cfm?parm1=5993

The AGA issued the following: “The AGA does not endorse CT colonography as a first-line colon cancer screening test. While AGA supports CT colonography as a screening option, colonoscopy is the definitive test for colorectal cancer screening and prevention. Colonoscopy is the only test that can both detect cancer at an early curable stage and prevent cancer by removing pre-cancerous polyps. At this time, while CT colonography may be another technology for colorectal cancer screening, many questions about CT colonography remain to be answered.”

ASGE. ASGE guideline: colorectal cancer screening and surveillance. Gastrointest Endosc 2006;63:546-557.

The American Society for Gastrointestinal Endoscopy published guidelines that were based on “a critical review of the available data and expert consensus.” They published the following excerpt:

“Virtual colonoscopy (VC), also known as CT colonography, involves helical CT scanning of the colon after bowel preparation and colonic distention. The technique for VC is considered in another guideline. Studies of VC have reported a sensitivity of 55% to 100% and a specificity of 94% to 98% for the detection of polyps measuring ≥10 mm and a sensitivity of 39% to 94% and a specificity of 79% to 92% for polyps at least 6 mm in size compared to colonoscopy. One prospective study of 614 patients with fecal occult blood, hematochezia, iron-deficiency anemia, or family history of colon cancer compared DCBE [double contrast barium enema] , VC, and colonoscopy. For lesions measuring ≥ 10 mm, the sensitivity of DCBE, VC, and colonoscopy was 48%, 59%, and 98% respectively. Higher patient acceptance of VC compared with colonoscopy has been suggested as a potential advantage of this procedure; however; comparative studies show no consistent patient preference. There are no studies demonstrating the efficacy of VC in reducing CRC incidence or mortality. There is also a concern regarding the associated radiation exposure, although VC may detect clinically important extracolonic findings. Virtual colonoscopy is not endorsed for CRC screening by multidisciplinary societal guidelines and is not covered by Medicare or private insurers. Cost-effectiveness analyses indicate that under most assumptions colonoscopy is more cost-effective than VC. Improvement in technology, training, and standardization of the technique are required before VC can be recommended for widespread screening. However, it may be useful for patients who refuse colonoscopy or who have had an incomplete colonoscopic examination. In general, patients with polyps detected on VC should undergo a complete colonoscopy. Although some authors advocate colonoscopy for any polyp identified on VC, 70 others suggest that colonoscopy should be selected for patients with polyps greater than 0.5 to 10 mm.

Recommendation. Virtual colonoscopy is an evolving technique and is not currently recommended as the primary method of screening for CRC.”

7. Public Comments

Initial 30-day comment period

CMS uses the initial public comments to inform its proposed decision. Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. CMS responses to initial comments are, as customary, incorporated into our analysis.

CMS received a total of 100 comments during the public comment period, which can be viewed on the website at http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=220.

Of the total 100 comments, 79 were in favor of amending the colorectal cancer screening policy to include coverage of the CTC screening test for average risk individuals. Twenty commenters were opposed to adding coverage of the new test as a colorectal cancer screening generally available to average risk individuals under Medicare Part B. One commenter did not offer a specific opinion on whether the new test should be covered for average risk individuals or not.

Of the total comments received, eight were from medical professional societies and other professional organizations and of the remaining 92, twenty-four included references and citations to clinical evidence. Six of the medical professional societies and other professional organizations also included references and citations to clinical evidence.

Comments from Professional Societies and Organizations

CMS received comments from the following: American Cancer Society (ACS), American College of Gastroenterology (ACG), American College of Radiology (ACR) (combined comments with the Society of Gastrointestinal Radiology and the Society of Computed Tomography and Magnetic Resonance), American Gastroenterological Association (AGA), American Society for Gastrointestinal Endoscopy (ASGE), American's Health Insurance Plans (AHIP), Medical Device Manufacturers Association (MDMA), and Medical Imaging and Technology Alliance (MITA).

Five commenters (ACS, ACR, AGA, MDMA, and MITA) recommended that CMS cover the use of CTC as a screening option once every 5 years for colorectal cancer for asymptomatic average risk adults age 50 and over under the Medicare program. Three of these commenters specifically indicated that CMS should require that physicians and other providers of such screening services meet certain minimum personnel, equipment, radiation dose, polyp reporting and referral, and other requirements as conditions of coverage for such colorectal cancer screening services. One of these commenters (AGA) specified that they would only support coverage for the CTC screening option if CMS requires that the provider meet the "necessary standards related to technology, training, and reporting of all polyps," and the new coverage is implemented through a Coverage with Evidence Development (CED) process.

Three commenters (ACG, ASGE, and AHIP) expressed the view or strongly suggested that it was premature at this time to support national Medicare coverage of CTC as a colorectal cancer screening test option for asymptomatic, average risk individuals until additional peer-reviewed scientific literature demonstrates that it meets quality standards and can be cost-effective. Two of these commenters offered that CMS should not proceed with its evaluation of this issue until more information has been published and data gaps have been filled on this subject, including the final ACRIN 6664 trial results and the United States Preventive Services Task Force's recommendations on screening for colorectal cancer (both subsequently published). One commenter recommended that if CMS decides to move forward in its analysis, it should "…follow its prior precedent and include the results of decision analytic modeling as a basis for evaluating both the clinical effectiveness and cost-effectiveness of any new strategy for colorectal cancer."

Comments with Evidence

Comments with evidence are public comments in which the commenter included references to publicly available information. There were 24 of these comments that were not previously summarized in the above section for professional societies and organizations. Seventeen of these commenters supported coverage of the new screening test; seven of these were non-supportive. Articles and information provided as evidence includes studies and information already mentioned.

Basic research studies and animal studies generally do not provide evidence of clinical benefit that is particularly pertinent to CMS. Review articles do not provide additional information. Unpublished, and therefore, non-peer-reviewed, information generally is accorded less weight than published and peer-reviewed material.

Test Performance

Most commenters in favor of coverage referred to either the multi-center trial (ACRIN 6664), the recent Pickhardt study (10/04/07), or both of those studies, and well as other studies, demonstrating that the CTC test was an effective screening for colorectal cancer that is were comparable to optical colonoscopy. Several of these commenters emphasized that the ACRIN study, which is the largest prospective trial to date in screening the asymptomatic, average risk population, demonstrated that CTC had a sensitivity of 90% and a specificity of 86% for adenomatous colorectal lesions of 1 cm or larger. One commenter also indicated that numerous large multi-center randomized clinical trials performed in multiple countries around the world in both academic and community settings have shown sensitivity and specificity very comparable to that of optical colonoscopy and noted that these results appeared to apply to a wide degree of practitioner settings.

Commenters opposed to coverage, however, raised questions regarding the performance of the test in detecting flat lesions (Soetikno) and small polyps less than 6 mm in size – especially outside of experienced academic centers. One of these commenters indicated that the available evidence did not support generalizing the results of the ACRIN trial and the Pickhardt study to other practitioner settings. Another commenter stated that despite the initial reports of the superior results by Pickhardt, et al., most follow-up trials have shown a significant miss rate for polyps below 1 cm which may be malignant. Another commenter noted that “Interestingly, in less publicized research in Clinical Gastroenterology Hepatology, Gupta and colleagues showed that radiologists often underestimate the size of polyps that they have seen, which means that even larger polyps may go unreported and undetected”. On the other hand, one commenter in favor of coverage stated that “There is a clear documented correlation between adenoma size and risk of malignancy raising the valid question of whether diminutive polyps are even worth resection at all (much less mentioning in a CTC study). (O’Brien M, et al.) The National Polyp Study. Gastroenteral 1990; 88:371-379.”

Radiation Concerns

Three commenters opposing coverage expressed concern regarding radiation risk with CTC tests. One commenter indicated that it was difficult to define precise risk estimates related to low doses of ionizing radiation exposure, but referred to one study that indicated that the radiation exposure from a single abdominal or chest CT may be associated with elevated risk of DNA changes and cancer formation. (Lobrich, 2005). This commenter added that the most recent update from a respected organization (unspecified by commenter) indicates that a single population device of 10 mSv is associated with a lifetime attributable risk for developing a solid cancer or leukemia of 1 in 1,000. Another commenter focused on the effects of multiple exposures to ionizing radiation during repeated CT tests at proposed intervals for CTC tests for colorectal cancer of once every 5 years.

Other commenters in support of coverage of CTC as a screening option for detecting colorectal cancer have stated that the risk of radiation exposure with the use of the currently low dose technique resulting in a radiation dose that is less than that of a double contrast barium enema (5mSv). One commenter referred to a recent study (Brenner, et al, 2005) that addressed the issue of radiation dose screening with the CTC test and concluded “that the benefit-risk ratio was high and that cancer risks were very low.” Brenner concluded “that potential lifetime cancer risk for one CTC test at 50 was 0.14% (007% if 70), which could be reduced by factors of five or ten with optimized low dose protocols.” In addition, one commenter indicated that “The ACRIN trial was performed with a low-dose CT technique yielding a total dose of about 5 mSv per exam . . .” and noted that this was an amount that the Health Physics Society considers a risk that is either nonexistent or “to small to be measured”.

Frequency Interval

Most of the commenters supporting coverage of CTC tests as a screening option for detecting colorectal cancer agreed with the recently issued joint guideline from ACS, ACR and the US Multi-Society’s Task Force on colorectal cancer, which recommends a screening interval of 5 years between negative CTC interpretations. One of these commenters indicated that this recommendation was based on the most recent data that was evaluated by ACS and appeared to be reasonable given that the current ACS recommendation for DCBE is 5 years and that for colonoscopy is 10 years. One commenter stated that the frequency interval should be based on an analysis of the ACRIN trial results. One commenter opposing coverage expressed concern regarding the frequency interval that would be used for the CTC test after a negative optical colonoscopy following a positive CTC test.

Extra-Colonic Findings

Several comments opposed to coverage of the CTC screening test raised concerns with regard to the detection and interpretation of extra-colonic findings that result from the scope of the CTC examination. One commenter referenced the recent ACS/MSTF colorectal caner screening guideline, which indicated that “Significant abnormalities” are detected approximately 8% of the time in the studies reported to date. This commenter noted that these scans can lead to more testing (e.g., x-rays, biopsies) which incur a considerable cost to the health care system as well as potential risks to the patient with uncertain benefits. A second commenter stated that “It should be feasible to launch studies of patients receiving CTC that will document more precisely the prevalence of extra-colonic findings and ascertain their clinical impact and the cost associated with their follow-up.”

Cost Effectiveness

Several commenters addressed the issue of the cost effectiveness of the CTC test as a screening option for CRC. One commenter opposed to coverage expressed concern that “The test is an expensive examination, being at least five times more expensive than the current radiographic imaging test for colon polyps, the double contrast barium enema” (DCBE) test. The commenter noted that in a recent comparison of CTC and DCBE, there was a significant difference in specificity of DCBE versus CTC for polyps >1 cm (99% versus 96%) (Johnson C. Gastroenterol Hepatol 2004;2:314-21). The commenter added that the specificity of CTC drops off significantly with the smaller size polyps. In a U.S. study of CTC using sensitivities of 82% and 91 % for 6-9 mm and 10 mm and greater polyps, respectively, compared to no screening at all, however, a second commenter in favor of coverage stated that compared to no screening at all, CTC is very cost effective at either 5 or 10 year intervals at $8, 000 - $17, 000 per life year prolonged. (Vijan et al, 2007).

Comments without Evidence

CMS received 73 comments without references and citations to clinical evidence. Thirteen in this category opposed coverage and one commenter did not express a preference relative to coverage, but suggested that the eligibility age for beneficiaries should be reduced to 40 years old.

Physicians and Other Health Care Professional

Of this category, CMS received comments without evidence from 39 physicians and other health care professionals. Twenty-seven of these commenters supported general coverage of CTC as a screening option for asymptomatic average risk individuals and twelve commenters did not.

Many of the commenters in favor of general coverage of the test expressed the view that screening reduces colorectal cancer mortality and that the most effective way of doing that is to screen individuals before there are any signs or symptoms of a problem. A number of these commenters stated that since colorectal cancer screening is under-used in the Medicare population there is a need for a quicker, more accurate, and user-friendly test such as the CTC test to be covered under the program. Commenters opposed to general coverage of the test raised concerns related to radiation exposure, the difficulty of detecting small and flat polyps, the question of whether to report and refer all polyps for treatment, cost effectiveness of this modality, and the quality of tests performed outside of experienced academic centers. . A number of these commenters, however, noted that they did favor coverage of CTC tests when used for diagnostic purposes for patients following failed or difficult colonoscopies for a variety of indications.

General Public

CMS received 34 comments from the general public, including patients, screening candidates, their families and other individuals with an interest in the prevention or early detection of colorectal cancer. Thirty-two of these commenters supported coverage of the new test, one did not, and one did not express a preference relative to coverage.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act §1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Congress has specifically authorized coverage of certain screening tests under Medicare Part B. Subject to frequency limits, certain colorectal cancer screening tests are payable under the Medicare statute even if the tests would not satisfy the "reasonable and necessary" provision of section 1862(a)(1)(A). § 1862(a)(1)(H). Colorectal Cancer Screening Tests have a benefit category under § 1861(s)(2)(R) and § 1861(pp) of the Act. Section 1861(pp) defines the term "colorectal cancer screening test" to include, "such other tests or procedures, and modifications to tests and procedures under this subsection, . . . , as the Secretary determines appropriate, in consultation with appropriate organizations." Specifically for colorectal cancer screening, under 42 C.F.R. § 410.37(a)(1)(v), CMS may use the NCD process to determine coverage of other types of colorectal cancer screening tests that are not specifically identified in the law or regulations as it determines to be appropriate, in consultation with appropriate organizations. CMS is using the authority under § 1861(pp)(1)(D) and 42 C.F.R. § 410.37(a)(1)(v) to determine whether the scope of the CRC screening benefit should be expanded to include coverage of the screening CT colonography test.

Our determination of whether CT colonography is an appropriate screening test under Medicare involves consideration of test parameters and net health outcomes. This analysis focused on the following questions:

A. Is the evidence sufficient to determine that CT colonography is a valuable screening test as described above for colorectal cancer for average risk Medicare individuals compared to optical colonoscopy?

To answer this question, we will consider the factors reported by Cochrane and Holland individually and then collectively to assess the value of CT colonography as a screening test.

Simplicity. CT colonography is a relatively simple test that can be performed on commercially available CT scanners. It does require full purgatory bowel prep similar to the bowel prep for colonoscopy. No sedation is used. Scanning is done with oral contrast and colonic insufflation, which some individuals may find discomforting.
Acceptability. In published studies, CT colonography was acceptable to the participants.

Accuracy. With current technology and recommended scan settings, CT colonography provides an accurate image of the colon when preparation is adequate compared to optical colonoscopy.
Cost. The cost and cost-effectiveness of screening tests are important to consider especially in environments with limited resources, increasing expenditures, and the availability of alternatives.. The consideration of cost in screening is widely accepted, especially when considering whether an additional colorectal cancer screening test is appropriate.

The cost effectiveness of CT colonography was specifically evaluated by Zauber and colleagues (2009) who reported: "Based on the analyses from three microsimulation models, screening for CRC with CT colonography every 5 years with referral of individuals with a 6 mm or larger lesion to colonoscopy provides a benefit in terms of life-years gained that is comparable to that of five-year flexible sigmoidoscopy with annual FOBT and slightly lower than colonoscopy screening every 10 years. The cost of CT colonography relative to the benefit derived and to the availability and costs of other CRC screening tests, would need to be in the range of $108 to $205 to be a cost-effective alternative to all other available screening modalities, and in the range of $179 to $237 to be cost-effective compared to colonoscopy screening with CMS payment of approximately $500 for colonoscopy without polypectomy and $650 for colonoscopy with polypectomy." Vijan and colleagues (2007) found similar results and concluded: "CT colonography is an effective screening test for colorectal neoplasia. However, it is more expensive and generally less effective than optical colonoscopy. CT colonography can be reasonably cost-effective when the diagnostic accuracy of CT colonography is high, as with primary 3-dimensional technology, and if costs are about 60% of those of optical colonoscopy. Overall, CT colonography technology will need to improve its accuracy and reliability to be a cost-effective screening option."

Precision (sometimes called repeatability). A number of studies have shown that CT colonography can detect large polyps ≥10mm consistently. The precision for polyps < 10mm has been more variable.
Sensitivity. The sensitivity of CT colonography compared to optical colonoscopy is dependent upon the type of CT scanner, collimation, use of 2D and 3D imaging, size of the polyp, adequacy of bowel prep, and training of the physician interpreting the images. Earlier studies using single slice CT reported varying degrees of sensitivity. In recent studies, multi-slice (at least 8 or 16) CT scanners have been the standard with collimation of 1.25mm or less and both 2D and 3D visualization. It is generally acknowledged that CT colonography cannot reliably detect or differentiate polyps < 5mm and most studies have specifically not reported results for these small polyps by design. For polyps ≥ 6mm, the reported per patient sensitivity by Pickhardt (n=1233) and Johnson (n=2531) was 88.7% and 78%, respectively. For polyps ≥ 10mm, the reported per patient sensitivity was 93.8% and 90%, respectively.
Specificity. As with sensitivity, the specificity of CT colonography compared to optical colonoscopy is dependent upon the type of CT scanner, collimation, size of the polyp and training of the physician interpreting the images. For polyps ≥ 6mm, the reported per patient specificity by Pickhardt (n=1233) and Johnson (n=2531) was 79.6% and 88%, respectively. For polyps ≥ 10mm, the reported per patient specificity was 96% and 86%, respectively.

Overall. The two studies by Pickhardt (2003) and Johnson (2008) provide the most substantial, recent evidence on CT colonography and were consistent in showing a reasonable sensitivity and specificity for polyps ≥ 10mm compared to optical colonoscopy. The results were not as good for polyps ≥ 6mm and may have contributed to the debate about the clinical significance of 6-9mm polyps and recommendations on how to deal with them. The current multi-society recommendation to refer these patients for colonoscopy is largely based on expert opinion given the lack of evidence on health outcomes. The study by Kim (2007) reinforced the notion that CT colonography can detect colonic polyps but, since all participants did not undergo colonoscopy, estimates of sensitivity and specificity were not obtainable from this study.

Based on these main studies and the consideration of the above factors, CT colonography using at least 8-16 slice CT scanners has sensitivity and specificity that are comparable to optical colonoscopy for polyps ≥ 10mm, and is cost effective when reimbursed at an amount in the range of $179 to $237 for representative populations. For polyps 6-9mm, the evidence is suggestive but less convincing given the lower sensitivity and specificity. CT colonography does not appear to have the ability to reliably detect small polyps < 6mm. This position is consistent with the MedCAC voting results.

However, a pivotal, overarching concern is the generalizability of these main study results to the Medicare population (Appendix A). The mean age of participants in these studies (57.8 years, 57 years and 58.3 years in the Pickhardt, Kim and Johnson studies, respectively) was considerably younger than the Medicare aged population (mean age of 75.5 years in 2007, not including disabled beneficiaries, available at: http://www.cms.hhs.gov/DataCompendium/16_2008_Data_Compendium.asp#TopOfPage). Specific subgroup analyses of participants ≥ 65 years of age were not reported in the published reports so other participant characteristics may also be different. No published study has focused on a population more representative of the Medicare population. Without specific data and evidence, it is unclear if the determination of the above factors would result in a similar conclusion. It is also unclear if the published study results are generalizable. Thus there is insufficient evidence to determine that CT colonography is a valuable screening test for colorectal cancer for average risk Medicare individuals compared to optical colonoscopy. Estimates of test parameters for older participants ≥ 65 years of age from published studies and/or new studies are needed to address this critical concern.

B. Is the evidence sufficient to conclude that the use of CT colonography for colorectal cancer screening for average risk Medicare individuals improves net health outcomes compared to optical colonoscopy?

This question addresses the key issue for screening raised by Cochrane and Holland (1971) when they noted that a physician should have “conclusive evidence that screening can alter the natural history of disease in a significant proportion of those screened.” Since Medicare already covers several effective CRC screening tests, evidence should also exist to show that the addition of a new test would increase overall CRC screening. If the addition of a new test only leads to duplicative tests (or layering of tests), switching from one test to another, and increase resource expenditure without increasing overall screening in the target population, then the addition of that new test does not improve health outcomes and would not be justifiable. In the determination of net health outcomes (net benefits and harms), several components of CRC and CT colonography need to be considered.

1. Size and Type of Polyp

Since CT colonography cannot reliably detect polyps < 6mm, the impact of these polyps in the intervening screening interval is important but unknown at this point. Since all polyps seen on optical colonoscopy are routinely removed, the natural history of these small polyps has not been well characterized. The majority of these very small polyps are likely to be benign; however, Lieberman and colleagues (2008) noted that 1.7% of polyps < 6mm had advanced histology. In addition to polyp size, the type of polyp is a factor. Nonpolypoid (flat, depressed or indented) colorectal neoplasms are very difficult to detect with CT colonography and are more common than originally believed in past accounts. In a study of asymptomatic and symptomatic veterans, Soetikno and colleagues reported that the prevalence of nonpolypoid colorectal neoplasms was 9.35% and noted that these “were relatively common lesions diagnosed during routine colonoscopy and had a greater association with carcinoma compared with polypoid neoplasms, irrespective of size.” Further research on the natural history of polyps < 6mm and nonpolypoid lesions and their health outcomes is needed.

2. Referral to Optical colonoscopy and Prevalence of Polyps

The rate of referral to optical colonoscopy for polypectomy is another important consideration when using an intermediate screening modality such as CT colonography which does not have therapeutic capabilities. Although the optimal referral rate is unknown, a relatively high rate of referral would limit the utility of CT colonography as a screening test since many individuals would then be subject to duplicative tests. The rate of referral is dependent upon test parameters, such as sensitivity and specificity, and the prevalence of polyps in the targeted screening population. If all individuals with polyps $\geq$ 6mm are referred to colonoscopy as recommended by current guidelines, the referral rates would be 29.7% in the 2003 Pickhardt study (mean age = 57.8 years), 12.9% in the 2007 Kim study (mean age = 57.0 years),, and 12% in the 2008 Johnson study (mean age = 58.3 years),. Whitlock and colleagues (2008) noted: “On the basis of a referral threshold of any polyp 6 mm or greater, these studies suggest that 1 in 3 to 1 in 8 persons screened with CT colonography would be referred for colonoscopy.”

No published screening study has focused on an older population, more representative of the Medicare population, nor has any study had sufficient power to evaluate this subgroup separately. However, polyp studies have shown that the proportion of individuals that have at least one polyp $\geq$ 6mm increases with age. In a colonoscopy screening study, Liebermann and colleagues (2008) found the proportion of screening individuals with at least one polyp $\geq$ 6mm to be 13.8% for individuals aged 50-59 years; 16.9% for individuals aged 60-69 years; 18.5% for individuals aged 70-79 years; and 20.5% for individuals aged 80 years and older. The test positive rate (true positives and false positives) and thus referral rate in Medicare aged screening populations need to be specifically determined by appropriately designed clinical studies, since results from younger populations are not generalizable to an older population.

The value of an intermediate screening test such as CT colonography that does not have therapeutic options may well be reduced or negated if there is a high rate of referral to optical colonoscopy leading to duplicative tests. Lieberman and colleagues (2008) noted: “If large proportions of patients will require colonoscopy after CTC, patients will need to understand the likelihood of requiring colonoscopy and the possible need for 2 bowel preparations. Further study is needed to examine the cost-effectiveness of CTC if 20% of patients will require colonoscopy.”

3. Extracolonic findings

Extracolonic incidental findings on CT colonography are common. In the 2 largest studies, the percentage of participants with extracolonic findings ranged from 58% (Kim, 2007) to 66% (Johnson, 2008). The proportion of patients with extracolonic findings that subsequently underwent additional evaluation was not reported in either study. The overall clinical importance of these findings in these specific screening populations is poorly understood. The psychosocial impact of detecting and evaluating extracolonic findings has also not been reported. The cost of investigating extracolonic findings ranged from an additional $13 to $248 per study participant. The studies at the lower end of the cost range (Gleucker, 2003; Chin, 2005;Yee, 2005; Flicker, 2008;) evaluated the costs of additional radiological tests in the short term and did not include intervention and treatment costs. The studies at the higher end (Xiong, 2006; Kimberly, 2008) included the costs of clinic visits, laboratory tests, procedures and follow-up over 12 to 24 months.

Since extracolonic findings are common, evidence based standards and guidelines on reporting, monitoring and subsequent evaluation of these findings are needed. Multi-site screening (aorta, lung, spine, etc.) during CT colonography has been raised as a potential future application; however, there is no evidence of benefit from these investigations and screening of these regions conducted in this manner is not recommended by the USPSTF or any professional organization. On whole body CT scanning, the FDA noted: “At this time the FDA knows of no data demonstrating that whole-body CT screening is effective in detecting any particular disease early enough for the disease to be managed, treated, or cured and advantageously spare a person at least some of the detriment associated with serious illness or premature death.”

Since individuals undergoing screening are asymptomatic by definition, the potential impact of extracolonic findings on net health outcomes needs to be determined prior to general use of this modality. Fletcher and Pignone (2008) highlighted this dilemma and raised the following question: “What is the responsible use of information that nobody asked for but once found is difficult to ignore?”

4. U.S. Preventive Services Task Force

Under § 1861(pp)(1) the Secretary is required to consult with appropriate organizations in considering additional colorectal cancer screening tests or procedures, or modifications to tests or procedures. One such organization is the USPSTF.[1] For colorectal cancer screening with CT colonography, the USPSTF concluded that “the evidence is insufficient to assess the benefits and harms of computed tomographic colonography and fecal DNA testing as screening modalities for colorectal cancer. (I statement)” Other appropriate organizations also share this view (see evidence section).

5. Radiation

The radiation exposure from CT colonography for colorectal cancer screening is a potential concern since individuals undergoing screening are asymptomatic of the target condition. Clearly there is a risk from radiation but how large or small the risk is over time has not been well established. The risk is likely to be greater with repeat use and younger initiation of screening CT colonography. The radiation dose for a set of 2 scans (typical supine and prone positions) has been estimated to be about 13 mSv (Brenner, 2005). As a reference, the estimated radiation dose for a posterior-anterior and lateral chest x-ray is between 0.06-0.25 mSv. The actual radiation dose at different facilities may vary due to scanner technology and scanner settings, regardless the actual radiation dose needs to be measured and recorded at the time of scanning to allow a better understanding of the effect of radiation over time. The radiation exposure from subsequent tests to evaluate extracolonic findings should also be estimated as well. Long term follow-up of specific screening populations may provide additional information on the radiation risk from CT colonography.

6. Health Outcomes

No published study has evaluated survival following participation in CRC screening with CT colonography. While no study has specifically evaluated survival, it may be possible to infer that the detection and removal of clinically important precancerous polyps may disrupt the natural progression to cancer. However, in the consideration of net health outcomes, the lack of data on small and flat lesions, referral rate for colonoscopy, extracolonic findings and radiation makes the consideration of health outcomes hypothetical at best. Also, no study has shown an increase in CRC screening after adding CT colonography as an option. Edwards and colleagues (2004) reported: “Community-based colorectal neoplasia screening with CT colonography was accompanied by a participation rate that compares favorably with that of similar screening programs.” Scott and colleagues (2004) reported: “Providing a choice of test did not increase participation.”

7. Overall Consideration

Overall, when considering potential benefits and potential harms, there is insufficient evidence to conclude that the use of CT colonography improves health outcomes in Medicare beneficiaries. Data on the health outcomes, potential benefits and harms from small lesions, extracolonic findings and radiation are needed from well designed clinical studies. In addition, with the higher prevalence of polyps in the older Medicare population, the rate of referral to optical colonoscopy is extremely important and also unknown at this point. If there is a relatively high referral rate, the utility of an intermediate test such as CT colonography is limited. This conclusion is also consistent with the USPSTF I statement for CT colonography, and the views of other appropriate organizations.

Coverage of CT colonography by other health plans and insurers is variable with some, such as CIGNA and Kaiser Permanente, providing screening coverage while others, such as Aetna and Anthem, providing coverage for diagnostic use or when colonoscopy is not technically possible. The Blue Cross Blue Shield Technology Evaluation Center (TEC) is in the process of publishing a final report on CT colonography. In their brief executive summary, (http://www.bcbs.com/blueresources/tec/press/ct-colonography-virtual.html), the TEC concluded that CT colonography met TEC criteria but this has not been translated into coverage policy at this point. The TEC further noted: “Given that much of the evidence supporting colorectal cancer screening is indirect, it is not so surprising that consensus groups reviewing the same evidence might come to different conclusions, as have the USPSTF and the ACS regarding CT colonography. Although both groups reviewed the same evidence and similar decision models to reach their conclusions, an editorial accompanying the USPSTF publication suggests that subtle differences in emphasis may underlie the differing conclusions. The USPSTF appears to put more emphasis on the potential unknown effects of radiation exposure and workups for extracolonic findings, taking a more longitudinal perspective.”

From the Medicare perspective, it is also important to emphasize that the populations served by other health plans and insurers are significantly younger than the Medicare population, and thus would likely have a lower prevalence of polyps, lower test positive rates and lower rates of referral for optical colonoscopy with polypectomy. In these younger populations, the results from the studies by Pickhardt (2003), Kim (2007) and Johnson (2008) would be more directly applicable. Unfortunately, the currently available evidence is not generalizable to the Medicare population.

C. Other Considerations

1. Colonoscopy as Reference Standard

Optical colonoscopy has been considered the reference standard for most studies on CT colonography. It has screening, diagnostic and therapeutic options with direct visualization of the colon and polypectomy. While colonoscopy can also miss polyps, the utilization of segmental unblinding appears to enhance comparisons. There is a small risk of colonic perforation (0.01% as reported by Niv and colleagues, 2007), mainly occurring in colonoscopies with polypectomy. However, colonoscopy remains the only acceptable method to remove colonic polyps and is associated with fewer deaths from colorectal cancer as noted by Baxter and colleagues (2008). They also noted that colonoscopy may miss polyps especially ones on the right side (ascending portion) of the colon. As with any test or procedure that requires specific preparation by the individual undergoing the test and specific training by the physician performing it, variability may exist between operators, sites and setting. It is thus extremely important that adequate bowel preparation is done and colonoscopists are appropriately trained.

2. CT Colonography Training and Experience

As with optical colonoscopy, CT colonography requires adequate purgatory bowel preparation and specific physician training. Kim and colleagues (2007) noted: “Accurate CT colonography with high sensitivity and specificity for polyps $\geq$ 6 mm in size depends on meticulous technique.” Whitlock and colleagues reported: “Differences in the experience and training of radiologist readers has been cited as the major factor underlying discrepant test accuracy estimates for CT colonography in nonscreening populations. Radiologists in nonacademic settings who read a validated set of 15 CT colonographies exhibited considerable individual variability in accuracy (53% to 93%), consistent with our findings from 2 smaller CT screening studies comparing readers, as well as from ACRIN, which used trained and certified readers. The challenges of adequately ensuring high-quality CT colonography readings are further illustrated by reports from ACRIN that half of the radiologists did not pass the initial certifying examination (after either 1.5 days of training or experience with $\geq$ 500 cases), although all did pass after further training. Clearly, specification, implementation, and monitoring of quality standards will be needed before widespread population screening with CT colonography.”

3. Health Disparities

As noted above, the incidence of polyps and colorectal cancer increases with age. Given the importance of this trend, Medicare currently covers several colorectal cancer screening tests and encourages active participation in colorectal cancer screening programs. As reported in the published literature black individuals have a higher incidence and mortality from colorectal cancer compared to white individuals; however, race was not specifically addressed in this proposed memorandum since subgroup data on CT colonography performance have not been published.

IX. Summary

CMS does not believe that the evidence is sufficient to conclude that screening CT colonography improves net health benefits for asymptomatic, average risk Medicare beneficiaries. While it is a promising technology, many questions on the use of CT colonography need to be answered with well designed clinical studies that focus on health outcomes for the Medicare population. Until the evidence is sufficient, CMS strongly encourages physicians and beneficiaries to participate in CRC screening by selecting one of the several CRC screening tests that are currently covered under Medicare (Section 210.3 – Colorectal Cancer Screening Tests, available at: http://www.cms.hhs.gov/manuals/downloads/ncd103c1_Part4.pdf).

X. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes the following:

The evidence is inadequate to conclude that CT colonography is an appropriate colorectal cancer screening test under § 1861(pp)(1) of the Social Security Act. CT colonography for colorectal cancer screening remains noncovered.

We are requesting public comments on this proposed determination pursuant to Section 1862(l) of the Social Security Act. After considering the public comments, we will make a final determination and issue a final decision memorandum. As with all national coverage analyses, the public may submit comments or additional evidence that cause us to reassess our evidentiary review and arrive at different conclusions. If that should occur during finalization of this decision memorandum and we determine that CT colonography is clinically effective, then we would need to determine, using current or additional cost information, if CT colonography is cost effective. We are asking for public comment on the cost effectiveness of screening CT colonography for the Medicare population if we were to alter our clinical decision.

Appendix A

General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Screening and Characteristics of Screening Tests

Screening refers to the detection of previously undetected disease or conditions through history, physical examination, or testing. When deciding what diseases to include in screening programs, several factors are typically considered such as the burden caused by the disease, the availability of an appropriate screening test, the availability of effective treatments and evidence that early treatment from early detection leads to better health outcomes.

Since screening tests attempt to identify unrecognized disease in asymptomatic individuals and are typically performed in general average risk populations, certain characteristics of screening tests should be considered, such as sensitivity (the proportion of people with the disease who have a positive test for the disease), specificity (the proportion of people without the disease the disease who have a negative test), simplicity, cost or cost-effectiveness, safety, availability and acceptability. Ideally, a screening test should have high sensitivity, high specificity, low cost, high safety, and high acceptability to both individuals and clinicians. High sensitivity is desirable since more cases will be identified and in turn fewer cases will be missed. Since positive results are usually further evaluated, high specificity is also desirable so fewer false positive results will be obtained and fewer individuals will be subsequently subjected to unnecessary and potentially harmful confirmatory tests and interventions.

In addition, the positive predictive value (PPV) of a screening test is frequently discussed. PPV refers to the probability of having a particular disease if the test result for the disease is positive; and takes into account the prevalence of the disease. Generally, the PPV of a screening test is usually low even if the screening test has a high sensitivity and specificity, since prevalence of the particular disease is usually low in asymptomatic screening populations. Likewise, the negative predictive value (NPV) of a screening test refers to the probability of not having a particular disease if the test result for the disease is negative.

Similar to costs, cost effectiveness or cost effectiveness ratios are also commonly considered for screening tests. Cost effectiveness analysis takes into consideration the “net cost of implementing an intervention with the effectiveness of the intervention” (Haddix AC, Teutsch SM, Shaffer PA, Dunet DO. *Prevention Effectiveness*. Oxford University Press, New York, 1996, ISBN 0-19-510063-8). Cost effectiveness is often expressed as net cost per net effectiveness. Commonly for cancer screening, cost effectiveness analyses have reported results as cost per life saved or cost per cancer averted. A ratio of $50,000 or less per life saved is often accepted by health economists as indicating that the intervention is “cost -effective.”

[1] In the Medicare Improvements for Patients and Providers Act (MIPPA), Pub. L. No. 110-275, §101 (July 15, 2008), Congress expanded the Secretary's authority to provide Medicare coverage of additional preventive services and screening tests that are, not otherwise described under Title XVIII, and are, among other things, recommended with a grade A or B (see following grading system) by the United States Preventive Services Task Force (USPSTF), an independent panel of experts in primary care and prevention that systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services. Congress has specifically recognized the expertise of the USPSTF and has given substantial weight to their recommendations in providing Medicare coverage. While this legislation does not affect coverage of colorectal cancer screening tests, which are "otherwise described under Title XVIII," it does support our belief that the USPSTF is an appropriate organization with whom to consult to determine whether the scope of the CRC screening benefit should be expanded to include coverage of the screening CTC test.

USPSTF 2008. Grade A: "The USPSTF recommends the service. There is high certainty that the net benefit is substantial." Grade B: "The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial." Grade C: "The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is moderate or high certainty that the net benefit is small." Grade D: "The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits." I Statement: "The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined."

[i] The coverage of screening colonoscopy was expanded by the Medicare, Medicaid, and SCHIP Benefits Improvement and Protection Act of 2000, § 103, Pub. L. No. 106-554 (December 21, 2000), to include beneficiaries at average risk every 10 years, effective January 1, 2002.

[ii] Individuals at high risk for colorectal cancer means an individual with (1) a close relative who has had colorectal cancer or adenomatous polyp; (2) family history of familial adenomatous polyposis; (3) family history of hereditary nonpolyposis colorectal cancer; (4) personal history of adenomatous polyps; (5) personal history of colorectal cancer; or (6) inflammatory bowel disease, including Crohn's disease and ulcerative colitis.

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